REMARKS

Claim 49 has been amended to recite a genomic library comprising nucleic acid from a combination of multiple organisms. Support for amended claim 49 is found on page 29, lines 9-12. Amended claim 49 and claims 12-24, 28, and 33 are pending. The amendments to the claims are indicated in the section entitled "Versions With Markings to Show Changes Made." A list of the now pending claims is provided in the section entitled "Pending Claims 12-24, 28,33, and 49, As Amended."

Claim Rejections - 35 U.S.C. §112, First Paragraph

Claims 20, 22 and 33 stand rejected for lack of written description under 35 U.S.C. §112, first paragraph, as containing subject matter not sufficiently described in the specification for reasonably conveying to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. The rejected claims are directed to methods of high throughput integrated genomics wherein at least one of the method steps is performed using a robotic system (e.g., claims 20 and 22) and to the robotic systems which perform the required steps (claim 33). The Examiner asserts that the data and examples provided in the specification do not demonstrate how the robotic systems are used to perform the steps recited in the rejected claims or which combinations of the robotic system are required for performing these steps.

Applicant respectfully traverses.

The Examiner has the initial burden of presenting the evidence or reasons establishing why the skilled artisan would not recognize a description of the invention defined by the claims in Applicant's disclosure. *In re Werthein*, 541 F.2d 257, 265, 191 USPQ 90, 98 (CCPA 1976); *Ex parte Sorenson*, 3 USPQ2d 1462, 1463 (Bd. Pat. App. &

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Inter. 1987). Applicant maintains that the Examiner has not met this burden and directs

the Examiner's attention to MPEP II.A (8th Edition, August 2001) §2163 stating:

> There is a strong presumption that an adequate written description of the
> claimed invention is present in the specification as filed. *In re Wertheim,*
> 541 F.2d 257, 263, 191 USPQ 90, 97 (CCPA 1976)....Consequently,
> rejection of an original claim for lack of written description should be <u>rare</u>.
> MPEP § 2163 (II.A).

The robotic systems and instrumentation necessary for making libraries of nucleic

acid variants, of introducing nucleic acid variants into cellular libraries, and of performing

phenotypic screening of cellular libraries, as required by claim 20, are described on page

36, line 38; page 37, lines 1-8; page 48, lines 14-40; page 49, lines 1-38; and page 50,

lines 1-3 of the specification, and in Figs. 1 and 2. For example, the instrumentation

which enables the monitoring of size, growth, and the phenotypic expression of specific

markers on cells is described on page 32, lines 34-39 and on page 33, lines 1-11. In

Example 1 of the specification (*e.g.,* page 49, lines 26-32), the use of CCD cameras for

monitoring cell growth and phenotypic expression and of automated colony pickers for

facilitating the rapid screening of desired clones is described. On page 44, lines 26-39 and

page 45, lines 1-17 of the specification, a variety of different phenotypic screens are

provided for screening target cells which contain the variant nucleic acid sequences. In

Example 5 (*e.g.*, page 55, lines 30-35) of the specification, the use of high-throughput

platforms for high-throughput enhanced homologous recombinant phenotypic screening is

also described.

The robotic systems and instrumentation necessary for making a plurality of cells

comprising mutant target nucleic acids, of adding libraries of candidate agents to cells, and

of determining the effects of the candidate agents on the cells (*e.g.,* page 41, lines 11-36;

page 42, lines 1-48; page 43, lines 1-38, and page 45, lines 19-38), as required by claim

22, are similarly provided on page 31, lines 11-39; page 32, lines 1-39; and page 33, lines

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1-34 of the specification, and in Figs. 1 and 2. For example, the robotic instrumentation provided in the specification may be used for producing nucleic acid libraries, for analyzing gene expression, and for the phenotyping and subsequent drug screening of nucleic acid libraries. Moreover, the robotic systems and instrumentation used for practicing the methods of high throughput integrated genomics, generally, as required by claim 33, are provided and described on page 31, lines 11-39, page 32, lines 1-39, page 33, lines 1-34 of the specification.

For the foregoing reasons, Applicant requests that the rejection of claims 20, 22, and 33 for lack of written description under 35 U.S.C. §112, first paragraph be withdrawn.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claim 12 (and claims 11-24, 28, 33, and 49-51 which depend therefrom) stands rejected under 35 U.S.C. §112, second paragraph, as failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner maintains that claim 12 is indefinite for failing to adequately define a first targeting polynucleotide substantially complementary to a fragment of a target nucleic acid and which is substantially complementary to a second targeting polynucleotide.

Applicant respectfully traverses the rejection.

Applicant directs the Examiner's attention to page 9, lines 18-28 of the specification. As indicated, the term "substantially complementary" refers to a sequence which is complementary to a sequence that substantially corresponds to a reference sequence. The term "substantially corresponds to" denotes a characteristic of a nucleic acid sequence with at least about 70 percent sequence identity, typically at least about 85 percent sequence identity, and preferably at least 95 percent sequence identity, compared

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to a reference sequence.   The percentage of sequence identity is calculated excluding any

small deletions or additions accounting for less than 25 percent of the reference sequence

(*see e.g.,* page 9, lines 1-23). Accordingly, "substantially complementary" refers to a

sequence having at least 70 percent, preferably 85 percent, and more preferably 95%

identity to a particular reference sequence. Applicant accordingly respectfully requests

reconsideration and withdrawal of the outstanding rejection of claim 12 for indefiniteness

under 35 U.S.C. §112, second paragraph.

The Examiner maintains that claim 20 is indefinite for failing to adequately

identify cell(s) or organism(s) with an altered phenotype using a robotic system.

Applicant reiterates that the use of a robotic system for performing phenotypic screening

on a cellular library, as required by claim 20, is described throughout the specification and

in the Examples, as previously described above and herein. Applicant accordingly

respectfully requests reconsideration and withdrawal of the outstanding rejection of claim

20 for indefinitenes under 35 U.S.C. §112, second paragraph.

The Examiner maintains that claim 22 is indefinite for failing to adequately

identify candidate agents which modulate the activity of mutant target nucleic acids using

a robotic system. Applicant reiterates that the use of a robotic system for determining the

effects of candidate agents on cells, as required by claim 22, is described throughout the

specification and in the Examples, as described above and herein. Applicant accordingly

requests reconsideration and withdrawal of the outstanding rejection of claim 22 for

indefiniteness under 35 U.S.C. §112, second paragraph.

The Examiner maintains that claim 33 is indefinite for failing to adequately set

forth the metes and bounds of a robotic system comprising a large number of components

and the combinations thereof.

Applicant respectfully traverses the rejection.

Applicant directs the Examiner's attention to page 31, lines 11-39 and page 32,

lines 1-32 providing that the any or all of the steps recited in Applicant's claims may be

completely or partially automated. The specification identifies on page 32, lines 29-32 of

the specification, a wide variety of components which may be used to practice Applicant's

invention (*e.g.,* one or more robotic arms, plate handlers for positioning microplates,

automated lid handlers for removing and replacing lids for wells on non-cross

contamination plates, tip assemblies for sample distribution with disposable tips, washable

tip assemblies for sample distribution, 96 well loading blocks, cooled reagent racks,

microtitler plate pipette positions, stacking towers for plates and tips, and computer

systems). The specification describes that full automation of enhanced homologous

recombination is accomplished with robotic instrumentation and thermal cycles for PCR

high-through put genomic and phenotypic assays in which automation enables high-

throughput gene cloning, high throughput phenotypic screening and the identification and

biovalidation of drug targets from multiple cell types and tissues (*e.g.,* page 31, lines 25-

28). The specification sets out a variety of tasks and steps which may be performed by the

fully automated robotic instrumentation described in the invention (*see e.g.,* page 31, lines

25-39). The components of the fully robotic systems, as described in the claims, are set

forth and provided in the specification on page 32, lines 1-8 and 28-30 and page 48, lines

32-40. For example, the robotic instrumentation may include microscope(s), plate readers,

CCD cameras, and a computer workstation (*see e.g.,* page 32, lines 34-39) which are

operative for enabling the monitoring of size, growth and phenotypic markers on cells,

target validation, lead optimization, data analysis, mining, organization, and the

integration of high-throughput screens using public and proprietary databases (*see e.g.,*

page 32, line 39 and page 33 lines 1-3).

In addition, the robotic work station described in the specification (*see e.g.,* Figure 1 depicting a robotic work station deck) may include one or more heating or cooling components (*e.g.,* Peltier systems) depending on which reactions and reagents are employed in the practice of the invention (*see e.g.,* page 33, lines 21-24). The work station may also include a central processing unit for communicating with a memory and a set of input/output devices (*e.g.,* keyboard, mouse, monitor, printer, etc.) through a bus (*see e.g.,* page 33, lines 26-28). A variety of different procedures may, moreover, be stored in the robotic system CPU memory and carried out using the robotic instrumentation described herein (*see e.g.,* Figure 2 depicting a flow chart outlining the automated robotic systems described in the invention).

For the foregoing reasons, Applicant has provided an adequate written description of the claimed robotic system and the components and combinations thereof. Applicant accordingly requests reconsideration and withdrawal of the outstanding rejection of claim 33 for indefiniteness under 35 U.S.C. §112, second paragraph.

The Examiner maintains that claim 49 is indefinite for reciting the limitation of "a genomic library comprising a combination of multiple organisms. Claim 49 has been amended to recite a genomic library comprising <u>nucleic acid</u> from a combination of multiple organisms. Support for amended claim 49 is found on page 29, lines 9-12. Applicant accordingly respectfully requests reconsideration and withdrawal of the outstanding rejection of claim 49 for indefiniteness under 35 U.S.C. §112, second paragraph.

The Examiner maintains that claims 50 and 51 are dependent on cancelled claim 1. Applicant points out that claims 50 and 51 are not a part of the pending claims in the instant application (*see e.g.,* section entitled "Pending Claims 12-24, 28,33, and 49, As

Amended"). Accordingly, Applicant respectfully requests reconsideration and withdrawal

of the outstanding rejection of claims 50 and 51 for indefiniteness under 35 U.S.C. §112,

second paragraph.

Claim Rejections - 35 U.S.C. §103(a) (*Sena, et al.* in view of *Cathcart, et al.*)

Claims 12 (and claims 13-18, 28, 33 and 49 which depend therefrom) stand

rejected under 35 U.S.C. §103(a) as being unpatentable over *Sena et al.* (U.S. Patent

5,948,653) in view of *Cathcart, et al.* (WO 91/16675). In particular, the Examiner states

that *Sena* teaches a method of detecting a duplex DNA target using RecA coated DNA

probe strands which are complementary to a first and second strand of target duplex DNA.

The Examiner maintains that although *Sena* fails to teach the detection of duplex DNA

using a robotic system, *Cathcart* corrects the deficiencies of *Sena* in that the reference

discloses a robotic system which performs biological procedures, including the isolation of

nucleic acids. The Examiner concludes that it would have been *prima facie* obvious to use

the *Cathcart* robotic system for performing the methods recited in *Sena* in the practice of

Applicant's invention.

Applicant respectfully traverses.

Claim 12 requires that enhanced homologous recombination compositions be

contacted with a library of target nucleic acid(s). As distinguished from Applicant's

invention, *Sena* neither teaches nor discloses a library of target nucleic acids. The

reference merely discloses DNA targets comprising viral lambda genomic DNA,

restriction digest fragments of viral lambda genomic DNA, or DNA targets prepared from

cultured cells (*see e.g.,* column 8, lines 44-68, column 9, line 1, column 14, lines 9-11,

column 27, lines 38-39, column 28, lines 5-7, 39-40, and 60-61, and column 29, lines 22

and 64-65). Accordingly, Applicant is unaware of any disclosure in *Sena* which teaches or describes target nucleic acids which comprise a library.

Cathcart teaches a robotic system for performing the steps of hybridizing probe to target nucleic acids and of capturing the resulting probe/target hybrid (*see e.g.,* page 47, lines 1-3). As distinguished from Applicant's invention, however, the reference fails to teach the utilization of enhanced recombinant techniques for identifying, isolating, cloning, and phenotypically screening a library of target nucleic acids.

For the foregoing reasons, *Sena* either alone or in combination with *Cathcart*, fails to teach all of the limitations recited in the claims. Accordingly, Applicant respectfully requests that Examiner's rejection under 35 U.S.C. 103(a) of amended claim 12 (and claims 13-18, 28, 33 and amended 49 which depend therefrom) be withdrawn.

Claim Rejections - 35 U.S.C. §103(a) (*Sena, et al.* in view of *Cathcart, et al.* and *Short, et al.*)

Claims 19 and 20 (which depend from claim 12) stand rejected under 35 U.S.C. §103(a) as being unpatentable over *Sena et al.* (U.S. Patent 5,948,653) in view of *Cathcart, et al.* (WO 91/16675) and *Short*. The Examiner states that although neither *Sena* nor *Cathcart* teach the production and screening of expression libraries of target nucleic acids, *Short* corrects the deficiencies of *Sena* and *Cathart* in that the reference discloses the production of expression libraries containing variant nucleic acids which are screened with candidate agents. The Examiner concludes that it would have been *prima facie* obvious to use the methods of making and screening clone libraries, as described in *Short*, in combination with the teachings of *Sena* and *Cathcart*, for practicing Applicant's invention.

Applicant respectfully traverses.

Sena and Cathcart are discussed above and herein. Applicant is unaware of any

disclosure in Sena which teaches a library of target variant nucleic acids. Cathcart fails to

teach the utilization of enhanced recombinant techniques for phenotypically screening a

library of target variant nucleic acids produced by the methods recited in the claims and

possessing the characteristics required by the claims. Short, moreover, teaches a process

for identifying clones having a specific activity of interest wherein gene expression

libraries (e.g. from a microorganism) are generated and the cellular libraries are exposed to

particular substrates and subsequently screened to identify clones which react to the tested

substrates. As distinguished from Applicant's invention, Short neither teaches nor

discloses a library of variant target nucleic acids wherein the members of the library are

contacted with enhanced homologous recombination compositions. The teachings of Sena

and Cathcart, as discussed herein, fail to correct the deficiencies of Short. Accordingly,

Sena, Cathcart, and Short, either alone or in combination, fail to anticipate Applicant's

claims. Applicant therefore respectfully requests that the Examiner's rejection under 35

U.S.C. 103(a) of dependent claims 19 and 20 be withdrawn.

Claim Rejections - 35 U.S.C. §103(a) (Sena, et al. in view of Cathcart, et al. and Ghai, et al).

Claims 21-24 (which depend from claim 12), stand rejected under 35 U.S.C.

§103(a) as being as being unpatentable over Sena et al. (U.S. Patent 5,948,653) in view of

Cathcart, et al. (WO 91/16675) and Ghai (U.S. Patent 5,955,269). In particular, the

Examiner maintains that Ghai teaches methods for screening for bioactive substances in

food which are capable of modulating the expression of disease-related genes. The

Examiner maintains that Sena in view of Cathcart and Ghai teach the methods that are

recited in dependent claims 21-24.

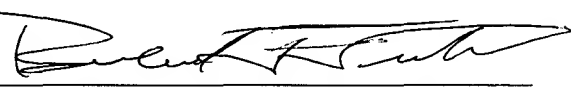*Sena* and *Cathcart* are discussed above and herein. *Ghai* teaches an assay system for screening nutraceuticals which are capable of modulating one or more genes that are associated with a disease or an undesirable condition (*see e.g.,* abstract). As distinguished from Applicant's invention, *Ghai* neither teaches nor discloses adding a library of candidate agents to a library of target nucleic acid variants as required by the claims. Accordingly, *Sena, Cathcart,* and *Ghai,* either alone or in combination, fail to anticipate Applicant's claims. Applicant therefore respectfully requests that the Examiner's rejection under 35 U.S.C. 103(a) of dependent claims 21-24 be withdrawn.

Conclusion

If upon, review, the Examiner feels there are additional outstanding issues, the Examiner is invited to direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

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VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Claims:

49.   (Amended) The method of claim 17, wherein said genomic library comprises
<u>nucleic acid from</u> a combination of multiple organisms.

Pending Claims 12-24, 28, 33, and 49 as Amended

12.   (Amended)   A method of high throughput integrated genomics comprising:

a)   providing a plurality of enhanced homologous recombination (EHR) compositions, wherein each composition comprises:

    i)   a recombinase;

    ii)   a first and a second targeting polynucleotide, wherein said first targeting polynucleotide comprises a portion substantially complementary to a fragment of a target nucleic acid and is substantially complementary to said second targeting polynucleotide; and

    iii)   a separation moiety;

b)   contacting said EHR compositions with a library of target nucleic acid(s) under conditions wherein said targeting polynucleotides hybridize to one or more target nucleic acids of said library; and

c)   isolating and cloning said target nucleic acid(s) wherein said isolating and cloning are performed using a robotic system.

13.   The method according to claim 12, wherein said target nucleic acid is a target gene.

14.   The method according to claim 13, wherein said target nucleic acid is a portion of said target gene.

15.   The method according to claim 12, wherein said target nucleic acid is a regulatory sequence.

16.   The method according to claim 12, wherein said target nucleic acid comprises single-polynucleotide polymorphisms.

17.   The method according to claim 12, wherein said library of target nucleic acids comprises all or part of a cDNA library, genomic DNA library, genomic DNA samples, or combinations thereof.

18.   The method of claim 17, wherein said genomic DNA samples are from one or more organisms.

19. The method according to claim 12 further comprising:

d) making a library of nucleic acid variants of said target nucleic acid;

e) introducing said library of nucleic acid variants into a cellular library; and

f) performing phenotypic screening on said cellular library.

20. The method according to claim 19 wherein at least one of said making, introducing and performing steps is performed using a robotic system.

21. The method according to claim 12 further comprising:

d) making a plurality of cells comprising a mutant target nucleic acid;

e) adding a library of candidate agents to said plurality; and

f) determining the effect of said candidate agents on said cells.

22. The method according to claim 21 wherein at least one of said making, adding, and determining steps is performed using a robotic system.

23. The method according to claim 21, wherein said mutant target nucleic acid is a gene sequence knock-out or a gene sequence knock-in.

24. The method according to claim 21, wherein said mutant target nucleic acid comprises an insertion, substitution, deletion or combinations thereof.

28. The method according to claim 12 further comprising sequencing said target nucleic acid.

33. The method of claim 12, wherein said robotic system comprises a computer workstation comprising a microprocessor programmed to manipulate a device selected from the group consisting of a thermocycler, a multichannel pipettor, a sample handler, a plate handler, a gel loading system, a gene sequencer, an automated transformation system, a colony picker, a bead picker, a cell sorter, an incubator, a light microscope, a fluorescence microscope, a spectrofluorimeter, a spectrophotometer, a luminometer, a CCD camera and combinations thereof.

49.   (Amended) The method of claim 17, wherein said genomic library comprises nucleic acid from a combination of multiple organisms.

49.   (Amended) The method of claim 17, wherein said genomic library comprises nucleic acid from a combination of multiple organisms.